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(54) Title: OLIGOPEPTIDE TRANSPORTERS

(57) Abstract

The present invention relates to di- and tripeptides and their use as pro-moieties to facilitate the transmembrane transport of drugs, in particular of small molecular weight drugs and more particularly poorly absorbed small molecular weight drugs.

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Oligopeptide Transporters

FIELD OF THE INVENTION

The present invention relates to di- and tripeptides and their use as pro-moities to facilitate the transmembrane transport of drugs, in particular of small molecular weight drugs and more particular poorly absorbed small molecular weight drugs.

BACKGROUND OF THE INVENTION

The oligopeptide transporter is expressed in mammalian small intestinal epithelia and a number of biomembranes, and is instrumental in the process of amino acid absorption via active uptake of digested di- and tripeptides from the gastrointestinal lumen (1, 2). This transporter is energized by a Na^+-independent H^+-gradient, which is generated within the acid microclimate located adjacent to the apical surface of jejunal microvilli (2, 3). As opposed to transport systems specific for single amino acids and sugars, the oligopeptide transporter has an immense number of potential di- and tripeptide substrates (4). Various types of peptidomimetics have been shown to serve as efficient substrates for the oligopeptide transporter, including β-lactam antibiotics (5-7), angiotensin converting enzyme inhibitors (8), and rennin inhibitors (6); yet, free amino acids or intact tetrapeptides are not substrates for this transporter (1, 2). Due to the fact that it displays such a broad affinity for a variety of structurally similar molecules, the oligopeptide transporter has attracted significant attention within the field pharmaceutics for its potential use as a drug delivery vehicle (9, 10). In both human (11) and rabbit (12) small intestine, a protein has been identified as one which is primarily responsible for di- and tripeptide absorption via a H^+ cotransport mechanism. Interestingly, these human and rabbit H^+/peptide cotransporters exhibit an extremely high degree of cross-species homology (11). Although it has yet to be fully characterized, a functionally similar version of the oligopeptide transporter is expressed and utilized by the

human adenocarcinoma cell line, Caco-2, once the monolayer is fully differentiated and polarized (3, 5, 7, 13). Several groups have described the valuable utility of conducting both uptake and transport experiments using confluent Caco-2 monolayers as a model system for screening potential oligopeptide transporter substrates (3, 5, 7, 13-15); thus, it may be possible to extrapolate information from these types of *in vitro* studies in order to predict the absorption of various compounds across the mammalian gastrointestinal tract (7, 15).

From the perspective of drug delivery, it may be possible to exploit substrates for the oligopeptide transporter to function as pro-moieties, thus enhancing the bioavailability of poorly absorbed drug compounds. This type of rational drug design has been suggested previously (9, 10); yet, to date, the use of a hydrolysis-resistant substrate in this manner has not been demonstrated. One conceivable tactic would be to introduce a D-configured amino acid within a dipeptide in efforts to circumvent the metabolic lability inherent to naturally occurring dipeptides (10, 14, 16). Several studies have demonstrated that the oligopeptide transporter displays a preferential affinity for L/L-configured dipeptides as opposed to L/D, D/L, and especially D/D combinations (10, 14, 17). The structural requirements of peptides and peptidomimetics influencing their ability to interact with the oligopeptide transporter have been investigated, e.g., cyclization (14), N-terminal α-amino modification (4, 8) and assessment of hydrophobic potential (4, 15); but, it has not yet been determined if covalent side-chain modification of one of the amino acids in a linear di- or tripeptide results in a loss of affinity for the oligopeptide transporter. According to the present invention it has surprisingly been found that esterification of the aspartic acid in D-Asp-Ala does not interfere with its ability to inhibit the uptake of [^{14}C]glycylsarcosine ([^{14}C]Gly-Sar), an enzymatically stable dipeptide having a high affinity for the oligopeptide transporter expressed in Caco-2 monolayers (16).

MATERIALS AND METHODS

[^{14}C]glycylsarcosine ([^{14}C]Gly-Sar, 60 mCi/mmol) and [^{14}C]Mannitol (56 mCi/mmol) were purchased from Amersham International (Buckinghamshire,

U.K.). Fetal bovine serum (FBS), Dubelcco's Modified Eagle's Medium (D-MEM), 100x non-essential amino acids (NEAA), solution, trypsin (0.25%)-EDTA (1 mM), penicillin (10,000 U/ml) and streptomycin (10,000 µg/ml) solution, and Hank's Balanced Salt Solution (HBSS) were purchased from Life Technologies (Roskilde, Denmark). 2-(N-morpholino)ethanesulfonic acid (MES), N-2-hydroxyethylpoperazine-N'-2-ethanesulfonic acid (HEPES), and Bovine Serum Albumin (BSA) were purchased from Sigma (St. Louis, MO, USA). Various dipeptides, amino acids, Boc-D-Asp(OtBu)-OH DCHA, Boc-D-Asp(OcHex)-OH, Boc-D-Asp(OBzl)-OH, and H-Ala-OtBu were purchased from Bachem Feinchemikalien AG (Bubendorf, Switzerland). HObt was purchased from Fluka, (Buchs, Switzerland), and TBTU was purchased from NovaBiochem (Laufelfingen, Switzerland). All solvents were obtained from Riedel-de Haën (Seelze, Germany; all analytical grade solvents used for HPLC analysis were obtained from Gerner & Seusen (Copenhagen, Denmark); and the Ultima Gold scintillation fluid used was purchased from Packard (Groningen, The Netherlands).

CELL CULTURE

Caco-2 epithelial cells were obtained from the ATCC (Rockville, MD), and were used between passages 21 and 40. They were seeded into tissue culture treated TranswellsTM (4.7 cm^2, 0.4 µ pore size; Costar Corp., Cambridge, MA) at a density of 10^5 cells/cm^2. Cells were maintained in a humidified 5% CO_2 in air atmosphere at 37°C, and were cultured in Dubelco's Minimal Essential Medium (D-MEM) supplemented with 10% fetal bovine serum (FBS), penicillin/streptomycin (100 U/ml and 100 µg/ml, respectively), 1% L-glutamine, and 1% NEAA. The growth media was replaced every other day, and apical and basal volumes were maintained at 1.5 ml and 2.5 ml, respectively. Confluent cell monolayers were obtained 14-17 days post-inoculation, with each well demonstrating a transmembrane electrical resistance (TEER) of between 500-600 ohms.cm^2 as measured by an epithelial voltohmmeter (EVOM, World Precision Instruments, West Haven, CT). Cell monolayers could be maintained at a constant resistance for at least 7 days without suffering leakage between apical and basal compartments (as determined by [^{14}C]Mannitol flux) or a loss in

TEER. The total amount of protein on each Transwell filter was calculated using the Lowry method to be 0.42 mg/cm^2.

UPTAKE AND TRANSPORT EXPERIMENTS

Uptake experiments were performed in pH-adjusted HBSS supplemented with 0.05% BSA. Prior to conducting uptake experiments, Caco-2 monolayers were first rinsed and then incubated with HBSS (apical media = 0.05% BSA, 10 mM Mes, pH 6.0; basal media = 0.05% BSA, 10 mM Hepes, pH 7.4) for 15 min at 37°C under a 5% CO_2 atmosphere in order to equillibrate the cells to the change in pH gradient. Next, [^{14}C]Gly-Sar (0.5 μCi), and in certain wells, inhibitors of various concentrations were added concomitantly to the apical media of the Caco-2 Transwells. Following either a 15 or 120 min incubation period, buffer was removed from both the apical and basal chambers and the cells were washed four times with ice-cold HBSS, pH 7. Following this washing step, the entire polycarbonate membrane was cut off of the Transwell support and placed into a scintillation vial, scintillation fluid was added, and then the cell-associated radioactivity was counted via liquid scintillation spectrometry. Transport experiments were performed similarly, but following the incubation period the basolateral media was removed and analyzed for the presence of either [^{14}C]Gly-Sar or [^{14}C]Mannitol (to assess paracellular permeabililty).

Synthesis of D-Asp-Ala, D-Asp(cHex)-Ala, and D-Asp(BZ)-Ala

Boc-D-Asp(OtBu)-OH: Boc-D-Asp(OtBu)-OH was liberated from its DCHA salt by standard procedure yielding a colourless oil which was used without further purification.

Boc-D-Asp(OtBu)-Ala-OtBu: 1.23 g Boc-D-Asp(OtBu)-OH (4.25 mmol) was dissolved in 20 ml fresh distilled DMF at room temperature together with 0.574 g HObt (4.25 mmol) and 1.365 g TBTU (4.25 mmol). The mixture was then

stirred at room temperature for 5 min before adding 0.772 g H-Ala-OtBu (4.25 mmol) and 1.648 g DIPEA (12.75 mmol). The resulting mixture was stirred for 2 hr at room temperature and then evaporated to dryness. The remainder was dissolved in 25 ml ethyl acetate and then extracted with 3 x 20 ml 10% $NaHCO_3$ in water, 3 x 20 ml 5% acetic acid in water v/v. The ethyl acetate phase was dried over $Na_2 SO_4$ and then evaporated under reduced pressure, resulting in a colourless oil. The oil was used directly without further purification.

H-D-Asp-Ala-OH: The oil was dissolved in 20 ml DCM and 20 ml concentrated TFA was added and the mixture stirred for 2 hr at room temperature. The solvent was then evaporated under reduced pressure and the resulting oil was extracted with 3 x 10 ml ether, which turned the oil into 600 mg crystals, 70% in overall yield. The purity was verified by TLC and HPLC and was found to be better than 98%. The product was identified by ^{1}H-NMR.

H-D-Asp(OcHex)-Ala-OH: H-Asp(OcHex)-Ala-OH was prepared using the above described procedure resulting in a 75% overall yield (910 mg). The purity was verified by TLC and HPLC and was found to be better than 98%, and the product was identified by ^{1}H-NMR.

H-D-Asp(OBzl)-Ala-OH: H-Asp(OBzl)-Ala-OH was prepared using the above described procedure resulting in a 59% overall yield (735 mg). The purity was verified by TLC and HPLC and was found to be better than 98%, and the product was identified by ^{1}H-NMR.

RESULTS

pH-Dependence of [^{14}C]Gly-Sar Uptake and Transport

In order to insure that H^+-dependent, carrier-mediated uptake was the mechanism by which [^{14}C]Gly-Sar was internalized and transported by the Caco-2 cells, the pH-dependency of [^{14}C]Gly-Sar uptake into and transport across the

monolayers was ascertained. Previous studies using the Caco-2 model have shown that optimal conditions for substrate uptake via the apical oligopeptide transporter require an apical pH of 6.0 and a basolateral pH of 7.4 (13); thus, these conditions were maintained for all controls in our experiments. As is shown in Fig. 1, the amount of uptake and transport of [^{14}C]Gly-Sar following a 2 hr incubation was 3.01 ± 0.11 and 0.98 ± 0.06 pmol/mg protein/min, respectively. When the apical pH was raised to 7.4, the degree of [^{14}C]Gly-Sar uptake and transport was significantly less, i.e., 1.72 ± 0.10 and 0.51 ± 0.13 pmol/mg protein/min, respectively. For the transport experiments, the values are corrected for [^{14}C]Mannitol flux across the monolayers, which was 0.06 ± 0.02 for the pH 6 and 0.11 ± 0.02 pmol/mg/min for the pH 7.4 experiments.

[^{14}C]Gly-Sar Uptake via the Oligopeptide Transporter is Inhibited by Various Dipeptides

The affinities of a variety of dipeptides and amino acids for the oligopeptide transporter, as determined by their relative ability to inhibit the uptake of [^{14}C]Gly-Sar into Caco-2 monolayers, were assessed (Fig. 2). The two tested L/L-configured dipeptides, Gly-Sar and Gly-Pro, inhibit the apical uptake of [14C]Gly-Sar by >90%. Four dipeptides having a D-configured amino acid in either the first or second position, i.e., D-Leu-Tyr, D-Val-Asp, Gly-D-Glu, and Gly-D-Asp, were also tested for their relative affinities for the oligopeptide transporter. These D/L- or L/D-configured dipeptides demonstrate a reduced affinity for the oligopeptide transporter relative to the L/L-configured dipeptides; nonetheless, they were all able to inhibit [^{14}C]Gly-Sar uptake by >75%. As an additional control, two L-amino acids, L-Tyr and L-Phe, were tested for their ability to inhibit [^{14}C]Gly-Sar uptake in an identical manner, and as is shown in Fig. 2, they were both unable to inhibit [^{14}C]Gly-Sar uptake to any significant degree.

D-Asp-Ala, D-Asp(cHex)-Ala, and D-Asp(BZ)-Ala Inhibit [^{14}C]Gly-Sar Uptake

D-Asp-Ala, D-Asp(cHex)-Ala, and D-Asp(BZ)-Ala (all 20 mM in the apical media)

were tested in order to assess their respective abilities to inhibit the apical uptake of [^{14}C]Gly-Sar into Caco-2 monolayers during either a 15 or a 120 min experiment. As is shown in Fig. 3, the extent of inhibition of [^{14}C]gly-sar uptake is >95% for all three compounds following 15 min of competitive inhibition, and >80% following 120 min of competitive inhibition. Following several [^{14}C]Gly-Sar apical uptake inhibition experiments using various concentrations of each compound as a competitive inhibitor, the IC_{50} values for D-asp-ala, D-asp(cHex)-ala, and D-asp(BZ)-ala were calculated and found to be 4.37 ± 0.02, 4.23 ± 0.08, and 3.20 ± 0.33 mM, respectively.

D-Asp(cHex)-Ala and D-Asp(BZ)-Ala Stability during Uptake Experiments

Using HPLC, the stabilities of D-Asp(cHex)-Ala and D-Asp(BZ)-Ala under experimental conditions were calculated. HPLC analysis of the apical media of Caco-2 cells containing the β-carboxyl modified D-Asp-Ala compounds demonstrates that both D-Asp(cHex)-Ala and D-Asp(BZ)-Ala are 100% stable under these conditions for up to 5 hr. The apparent permeability of D-Asp(cHex)-Ala and D-Asp(BZ)-Ala was also calculated. In order to insure that an equillibrous mixture was attained, samples from the aqueous phase were submitted for HPLC analysis at both 8 and 24 hr. These experiments were performed in triplicate and the partition coefficient (P) was calculated using Equation 1:

Equation 1. $P = (C_i - C_w)/C_w \times V_w/V_o$

where C_i and C_w represent the concentration of D-Asp(cHex)-Ala and D-Asp(BZ)-Ala in the aqueous buffer phase before and after distribution, respectively; V_w represents the volume of the aqueous phase; and V_o is the volume of the octanol phase. The log P values for D-Asp(cHex)-Ala and D-Asp(BZ)-Ala were calculated to be -0.17 ± 0.01 and 0.15 ± 0.09, respectively; these values represent the means of N = 3 experiments ± S.D. D-Asp-Ala could not be detected via HPLC due to its lack of retention on the column used.

Thus, its log P values could not be determined.

There was no significant difference in the concentration of either compound in the aqueous phase 8 and 24 hr after rotation was initiated, indicating that equillibrium was indeed reached after 8 hr. No degradation products were seen in the chromatogram following 24 hr of rotation; thus, both D-Asp(cHex)-Ala and D-Asp(BZ)-Ala are completely stable for the duration of the uptake experiments.

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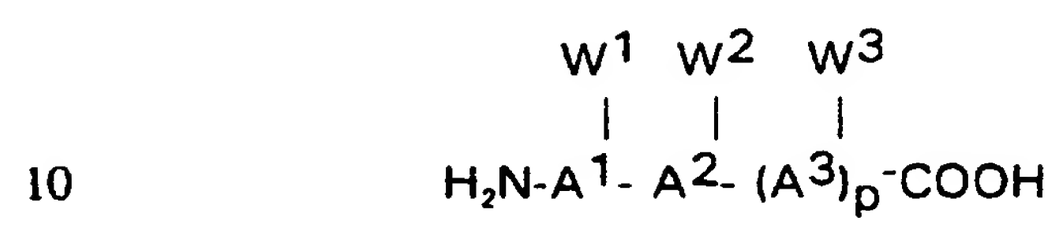
CLAIMS

1. A compound of general formula I



wherein

p is 0 or 1;

A^1 , A^2 and A^3 are natural or modified amino acids,

when p is 1, at least one of W^1, W^2 and W^3 are a residue of a pharmaceutically useful agent and the others are hydrogen,

when p is 0, W^1 is a residue of a pharmaceutically useful agent and W^2 is hydrogen or both W^1 and W^2 are pharmaceutically useful agents.

2. A compound of formula I wherein A^1 , A^2 or A^3 intended for linkage of the pharmaceutically useful agents are selected from the group consisting of Asp, Glu, Asn, Gln, Lys, Orn, Cys, Tyr, Thr and Ser.

3. A compound of formula I wherein A^1 or A^2 are natural amino acids in their D or L configuration or modified amino acids.

4. A compound according to claim 1 wherein A^1 , A^2 or A^3 are D-Asp or MeGly.

5. A compound according to claim 1 wherein at least one of W^1, W^2 and W^3 are a residue of a poorly absorbed pharmaceutically useful agent and the others are hydrogen.

6. A compound of formula I wherein p is 0 and A^1 and A^2 is selected from the group consisting of L-Asp-L-Ala, L-Lys-L-Ala, L-Cys-L-Ala, L-Ala-L-Asp, L-Ala-L-Lys, L-Ala-L-Cys, L-Asp-L-Gly, L-Lys-L-Gly, L-Cys-L-Gly, L-Gly-L-Asp, L-Gly-L-Lys, L-Gly-L-Cys, L-Asp-L-MeGly, L-Lys-L-MeGly, L-Cys-L-MeGly, L-MeGly-L-Asp, L-MeGly-L-Lys, L-MeGly-L-Cys, D-Asp-L-Ala, D-Lys-L-Ala, D-Cys-L-Ala, D-Ala-L-Asp, D-Ala-L-Lys, D-Ala-L-Cys, D-Asp-L-Gly, D-Lys-L-Gly, D-Cys-L-Gly, L-Asp-D-Ala, L-Lys-D-Ala, L-Cys-D-Ala, L-Ala-D-Asp, L-Ala-D-Lys, L-Ala-D-Cys, L-Gly-D-Asp, L-Gly-D-Lys, L-Gly-D-Cys, L-Orn-L-Ala, L-Ala-L-Orn, L-Orn-L-Gly, L-Gly-L-Orn, L-Orn-L-MeGly, L-MeGly-L-Orn, D-Orn-L-Ala, D-Ala-L-Orn, D-Orn-L-Gly, L-Orn-D-Ala, L-Ala-D-Orn, L-Gly-D-Orn.

7. A peptide of the general formula II:

$$H_2N\text{-}A^1\text{-}A^2\text{-}(A^3)_p\text{-}COOH$$

wherein p, A^1 A^2 and A^3 are defined as in claim 1.

8. The use of a compound of the general formula II

$$H_2N\text{-}A^1\text{-}A^2\text{-}(A^3)_p\text{-}COOH$$

wherein p, A^1 A^2 and A^3 are defined as in claim 1, for transport of pharmaceutically useful agents.

9. The use according to claim 8 wherein the pharmaceutically useful agent is poorly absorbed in its free form.

10. The use according to claim 8 wherein the pharmaceutically useful agent is selected from Fluorouracil or 6-Mercaptopurine.

FIGURE 1

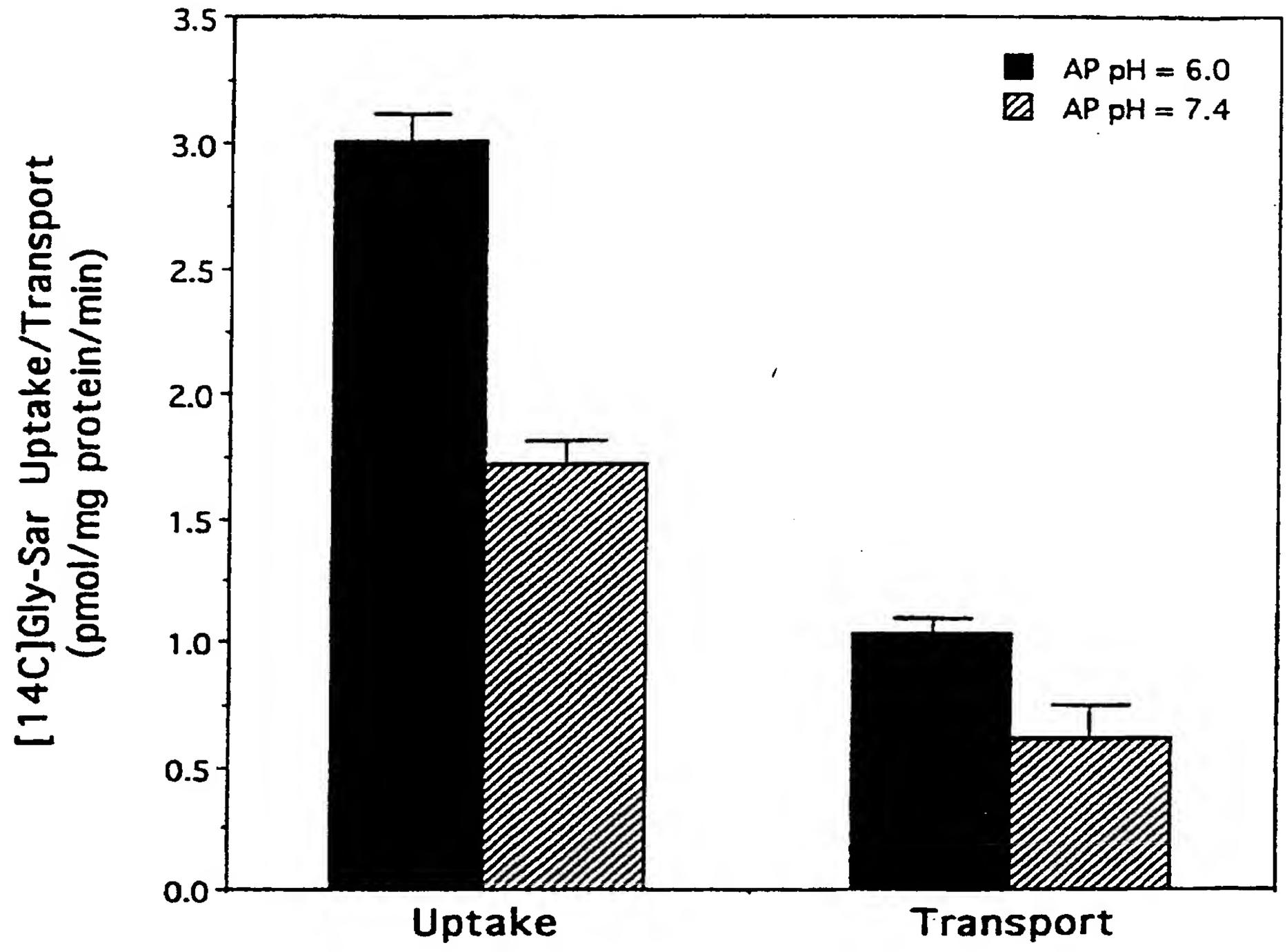


FIGURE 2

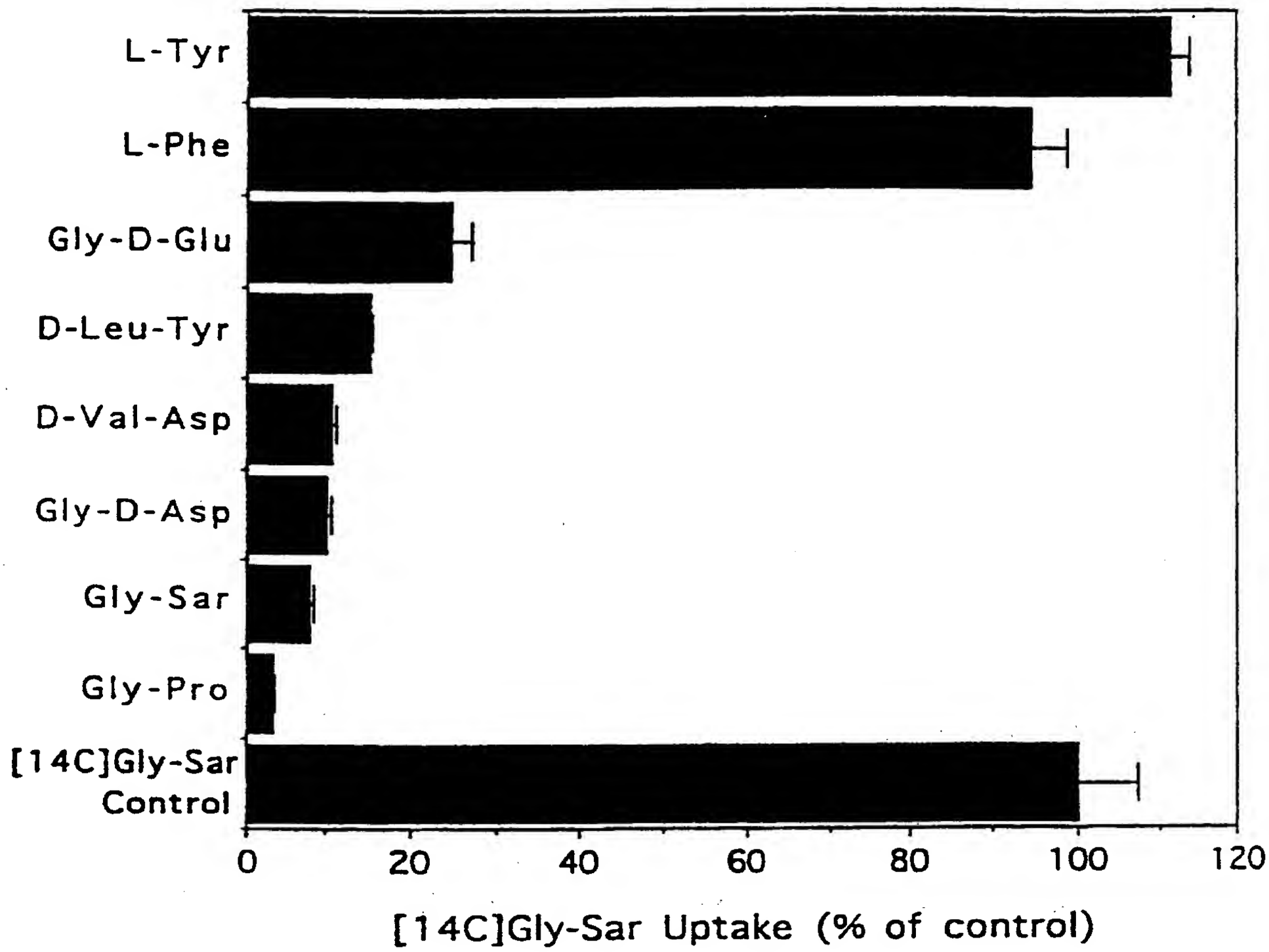
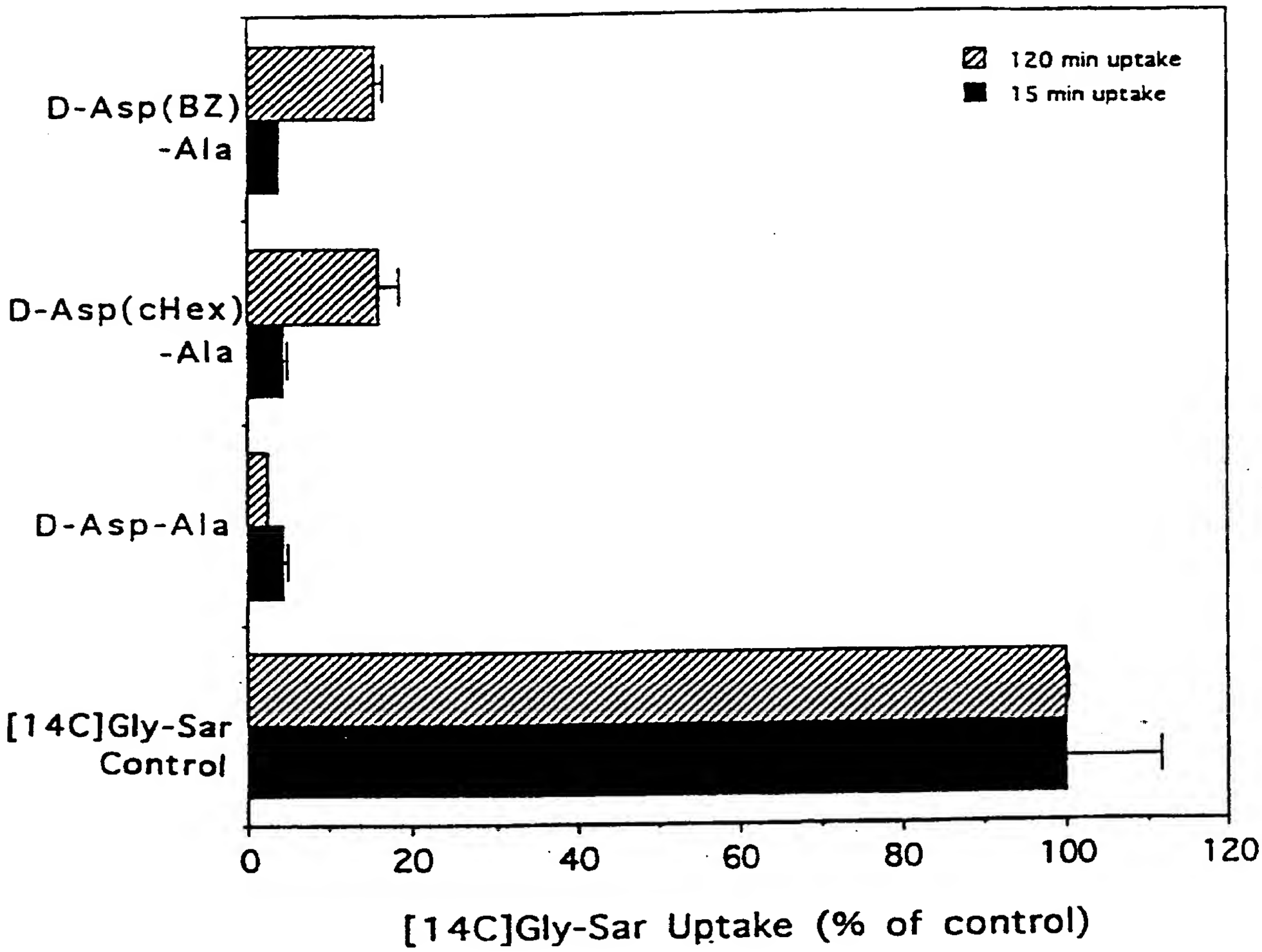


FIGURE 3



INTERNATIONAL SEARCH REPORT

International application No.
PCT/DK 97/00312

A. CLASSIFICATION OF SUBJECT MATTER

IPC6: C07K 5/06, C07K 5/08, C07K 5/02, A61K 47/48
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC6: C07K, A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

REG, CAPLUS, HEDLINE, WPI, EMBASE, IFIPAT

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 9605863 A1 (LA REGION WALLONNE), 29 February 1996 (29.02.96) ---	7-10
X	DRUG DELIVERY, Volume 1, 1993, PHILIP L. SMITH ET AL, "Exploitation of the Intestinal Oligopeptide Transporter to Enhance Drug Absorption", page 103 - page 111, See p. 105-106 --- --------	7-10

☐ Further documents are listed in the continuation of Box C. ☒ See patent family annex.

* Special categories of cited documents:
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Date of the actual completion of the international search	Date of mailing of the international search report
3 November 1997	05 -11- 1997
Name and mailing address of the ISA/ Swedish Patent Office Box 5055, S-102 42 STOCKHOLM Facsimile No. +46 8 666 02 86	Authorized officer Carolina Gomez Lagerlöf Telephone No. +46 8 782 25 00

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INTERNATIONAL SEARCH REPORT

Information on patent family members

01/10/97

International application No.
PCT/DK 97/00312

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9605863 A1	29/02/96	AU 3248695 A	14/03/96
		BE 1008581 A	04/06/96
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